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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,297	02/13/2002	Masako Yajima	219451US0	3488

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,297	YAJIMA ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT FOR PRIORITY, IDS, STATUS OF THE APPLICATION AND CLAIMS

1. Acknowledgment is made of Applicant's claim priority based on Japanese Application No. 2001-038486 having a filing date of 2/15/01. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file. The information disclosure statement (IDS) and Form PTO-1449 filed 5/7/02 are acknowledged, entered and considered. Claims 1-8 are present for examination.

THE SPECIFICATION, CLAIMS AND ABSTRACT ARE A LITERAL TRANSLATION

2. A substitute specification including claims and abstract in proper idiomatic English and in compliance with 37 CFR 1.52(a) and (b) is required. The claims are generally narrative and indefinite and fail to conform to current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

NUMEROUS ERRORS IN THE SPECIFICATION

3. 35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms, which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or

verbose terms used in the specification are: pages 1, 8, 10 and 13 are fragmented sentences in general; page 1, first paragraph, lines 3-5, "...inflammatory symptoms caused by lipopolysaccharide that are brought in bacterial infection, etc....."; page 1, last paragraph, line 1, "Among these antimicrobial materials"; page 8, first paragraph, lines 6-8, "...early recover a usual level of blood neutrophils, and suppress increase of neutrophils"; page 10, lines 1 and 2, "...as a sample for measurement of proteins until the measurement."; and page 13, second paragraph, lines 10 and 11, "....lactoferrin was not administered but LPS given".

OBJECTION TO THE SPECIFICATION

4. The disclosure is objected to because of the following informalities: On page 6, line 2, in the recitation "exdation". It is believed to be typographical error. Amendment of the specification to recite "exudation" is suggested. Appropriate correction is required.

CLAIMS REJECTION-35 U.S.C. 112 1st PARAGRAPH

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure, which is not enabling. Lipopolysacharide-induced inflammation is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The specification discloses on Figures 1-7 and Examples 1-5 a method for alleviating symptom resulting from lipopolysaccharide-induced (LPS-induced) inflammation from gram-negative bacteria by administering lactoferrin (human-type lactoferrin and bovine-type lactoferrin). Claims 1-8 as currently drafted are directed to a method for alleviating symptom resulting from inflammation by administering orally or parenterally human-type lactoferrin at various dosages as recited in the claims. The language of the specification (i.e., all the Figures and Examples including Field of the Invention in the specification) makes it clear that the limitation (i.e., LPS-induced inflammation) is critical for the invention to function as intended. Thus, the disclosed critical limitation of LPS-induced inflammation in the instant specification is missing from independent claim 1. Therefore, incorporating the critical limitation (i.e., LPS-induced inflammation) at least in independent claim 1 would obviate this rejection.

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The syntax of claim 1 is indefinite in the recitation "alleviating symptom", "giving a person orally or parenterally" and "an agent comprising". Amendment of the claim to recite " A method for alleviating symptoms from inflammation comprising administering to a person orally or parenterally an effective amount of human-type lactoferrin for a time and under conditions effective to alleviate said symptoms" is suggested.

Claim 2 recites "from the group consisting accumulation of body fluid....., accumulation of blood albumin....". It is not clear what is the difference between "body fluid" and "albumin" in a Markush format claim. It appears to be genus and species situation. Appropriate correction is required.

Claims 3-7 are indefinite in the recitation "in terms of lactoferrin" because it is not clear whether the claims refer to human-type lactoferrin or bovine-type lactoferrin or other type of lactoferrin. Appropriate clarification is required. Further, the phrase "in terms of" is superfluous. Deletion of this phrase is suggested.

Claim 8 is indefinite and confusing in the recitation "wherein the agent is given in a form of medicine or food" because it is not clear how the agent is given or administer? Is it ingested or injected or administered as a medicinal formulation? Also, it is not clear at what condition it is given as a form of food. Further the claim appears to be redundant to claim 1 because the formulation of claim 1 could be given or administered in a form of medicine or food. Appropriate clarification is required.

CLAIMS REJECTION-35 U.S.C. § 103(a)

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 8-165248 (English Machine-Assisted Translation) taken with Elass-Rochard et al. (Infection and Immunity, Vol. 66, No.2, pp. 486-491, February 1998).

The reference of JP 8-165248 ('248 patent) teaches the administration of an effective amount of lactoferrin and its derivative as an active agent for suppressing inflammation caused by endotoxin LPS-derived from gram-negative bacteria, wherein the lactoferrin is administered in the form of oral agent, injection (e.g., parenterally), eye

drop, or quasi-drug (e.g., mouthwash), cosmetic, food (e.g., chewing gum), etc. Depending on its use, the dosage ranges and mode of administration of the lactoferrin varies, for example, single dose of oral administration ranges from 1000 mg/kg to 4000 mg/kg or more; parenterally from 1 mg/kg to 50 mg/kg and as such overlaps with the dosage ranges claimed in claims 3-7 (i.e., 0.1 mg/kg to 1000 mg/kg). Thus, the reference clearly discloses the administration of lactoferrin as an active agent to suppress inflammation resulting in alleviating symptoms caused from LPS-induced inflammation due to acute inflammation or sepsis of the human by gram-negative bacteria (See e.g., pages 4, 5, 10, 13-15 and 25) as directed to claims 1-8.

The reference of '248 patent differs from claims 1-8 in not teaching the use of human-type lactoferrin for alleviating symptom from LPS-induced inflammation and the generation of tumor necrosis factor alpha (TNFα). However, the secondary reference of Elass-Rochard discloses the use of human-type lactoferrin (hLf) *in vitro* to inhibit endotoxin interaction with CD14 by competition with LPS-binding protein (See e.g., the Title). On page 486, first paragraph, left column, the reference states that it is known LPS are potent activators of the immune system. They stimulate host cells, mainly monocytes/macrophages and neutrophils, to produce endogenous mediators such as cytokines. On page 486, first paragraph, right column, the reference continues by stating that *in vivo*, hLf also regulates the release of TNF-α and protects mice against a lethal dose of *E. coli*. Thus, clearly showing that use of hLf increases blood neutrophils and generates TNF-α, and as such meet the limitation of claim 2. On page 489, under discussion, the reference states that the ability of hLf to form complexes with LPS and

thus to inhibit the LPS-induced release of cytokines by mononuclear phagocytes makes it a potentially important molecule in the inflammatory response. On page 490, last paragraph, the reference concludes by stating that Lf released from neutrophilic granules could neutralize the excess of LPS at the site of inflammation and protect the host against the excessive release of cytokines, and suggests that due to its high affinity for LPS, Lf could, *in vivo*, absorb small amounts of LPS. Further, *in vivo* studies are needed to investigate whether Lf could directly overcome the LBP-mediated activation of cells in the host and modulate the CD-14-independent LPS signal pathways.

With respect to the dosage ranges and mode of administrations, the ranges and mode of administration disclosed by the primary reference and claimed by Applicant overlap in scope as discussed above, and as such, the selection of the appropriate dosages and route of administration would have been *prima facie* obvious because where general conditions of claims are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges or situations by routine experimentation.

Further, as acknowledged by Applicant on page 2, paragraph 2 in the instant specification, it is known in the art that during sepsis caused by gram-negative bacilli, decline in blood albumin concentration, decrease of lymphocytic leukocytes, and increase of neutrophil occur. Also, on page 4, Applicant acknowledges that bovine-type lactoferrin has been used to demonstrate an effect of alleviating various symptoms, which appear after infection. Thus, in view of these and in view of the combined teachings of the prior art, particularly, the suggestion of the secondary reference of potential advantages of using hLf as discussed above, one of ordinary skill in the art

would have been motivated at the time the invention was made to employ human-type lactoferrin for treatment or alleviating symptoms resulting from LPS-induced inflammation of human because of the expected species to species reaction. Use of lactoferrin from the same species (i.e., human lactoferrin to human) will decrease antigenicity and allergy induction, and as such, less toxicity occurs which will not trigger immunoreactions resulting from antigenicity. Therefore, claims 1-8 are *prima facie* obvious over the combined teachings of the prior art, absent of sufficient objective factual evidence or unexpected results to the contrary.

CITATION OF RELEVANT PRIOR ART

8. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure:

Martins et al. (Clinical and Diagnostic Laboratory Immunology, Vol. 2, No. 6, pp. 763-765, November 1995) disclose the correlation of the neutrophil marker lactoferrin with inflammation in different body fluids including blood, gingival swab specimens, and saliva.

CONCLUSION AND FUTURE CORRSPONDANCE

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low can be reached on (571) 272-0951. The appropriate fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications..

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Christopher S.F. Low

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AAM Mohamed/AAM

June 25, 2004